Remarks:

Claims 40-60 have been rejected. Claims 1-39, 41, 48 and 55 are canceled. Applicant respectfully traverses the rejection of claims 40,42-47,49-54 and 56-60 in view of the arguments and amendments herein.

Rejections under §112

Claim 60 was rejected under §112. Claim 60 has been amended for clarity to comport with the disclosure. Applicant respectfully submits that the objection has been traversed by amendment.

Rejections under §103

Claims 40-45 and 47-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yasuda et al (Nature 2001) in view of Sonnichsen (Physical Review Letter Pub 112002) (as evidenced by Mock (Nano Letters Pub 412002)) and in further view of Pettingell et al (US Patent 6449088 Filed 1993). Claims 41, 48 and 55 are canceled.

Further, Claims 54-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yasuda et al (Nature 2001) in view of Sonnichsen (Physical Review Letter Pub 112002) (as evidenced by Mock (Nano Letters Pub 412002)). Claim 55 is canceled.

Further, Claims 46 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yasuda et al (Nature 2001) in view of Sonnichsen (Physical Review Letter Pub 112002) (as evidenced by Mock (Nano Letters Pub 412002)), and Pettingell et al (US Patent 6449088 Filed 1993) as applied to claims 40 and 47 above and in further view of Felder (US Patent 6232066). In view of the arguments and amendments herein, applicants respectfully traverse these rejections.

A brief discussion of the prior art follows:

Yasuda is cited for disclosing attaching a nanobead to an F1-ATPase motor, rotation using a nanobead and imaging with laser. However, Yasuda shows bonding to a rotating arm with biotin and streptavidin and no target matching DNA linkage is shown.

Sonnichsen is cited for disclosing gold nanorods. As evidenced by Mock a property of a nanorod is to alternately produce red and green polarized light when illuminated with polarized white light along the axes. No target matching DNA linkage is shown in Sonnichsen or Mock.

Pettingell et al. discloses using polarizing microscopes which use polarizers.

Felder is cited for disclosing oligonucleotide links as an anchor. No target matching DNA linkage between a rotating molecular motor and a nanoparticle suitable for causing the nanoparticle to rotate is discussed. Moreover, Felder differs strikingly from the instant invention for many reasons. As one example, Felder requires "a surface comprising multiple spatially discrete regions, at least two of which are substantially identical..." (Claim 1). No such spatially discrete regions are required in the present invention. In fact Felder needs multiple copies of these spatially discreet regions as stated in his specification "The spatially discrete regions of the invention are present in multiple copies. That is, there are at least two, preferably at least twenty, or at least about 24, 50, 96, 256, 384, 864, 1536, 2025, or more, etc.," (See, for example, Fig. 1 and Fig. 2). Felder does not address molecular motors or gold nanorods. Given that only the present invention teaches linking in order to effect rotation of gold nanorods, the present invention including claims 40,42-47,49-54 and 56-60 are patentable over the references whether taken singly or in any combination.

Claims 40,42-47,49-54 and 56-60 are allowable under the *Graham* factors for non-obviousness

Basic Factual Inquiries of Graham v. John Deere Co. (Ref. MPEP § 2141):

> As reiterated by the Supreme Court in *KSR*, the framework for the objective analysis for determining obviousness under 35 U.S.C. **103** is stated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows:

> (A) Ascertaining the differences between the claimed invention and the prior art; and
>
> (B) Ascertaining the differences between the claimed invention and the prior art; and
>
> (C) Resolving the level of ordinary skill in the pertinent art.
>
> ...Objective evidence relevant to the issue of obviousness must be evaluated by Office personnel. *Id.* at 17-18, 148 USPQ at 467. Such evidence, sometimes referred to as "secondary considerations," may include evidence of **commercial success, long-felt but unsolved needs, failure of others, and unexpected results**. The evidence may be included in the specification as filed, accompany the application on filing, or be provided in a timely manner at some other point during the prosecution (emphasis added).

Relative to the instant application the facts bear out that the claimed invention has solved a long-felt but unsolved need that has been widely accepted by the scientific community. The inventors, and particularly Dr. Wayne Frasch have been recognized as making a significant contribution in the field by other renowned experts in the field.

As just one example, Yuan and Berg of Harvard University state: "To work at lower loads, the most promising method appeared to be the **gold nano-rod technique used by Wayne Frasch to study rotation of the F1 ATPase** [5] (emphasis added). Yuan and Berg, "Following the Behavior of the Flagellar Rotary Motor Near Zero Load," Experimental Mechanics, published online: 09 Sept. 2009. Citing Spetzler D, York J, Daniel D, Fromme R, Lowry D, Frasch W (2006) "Microsecond time scale rotation measurements of single F1-ATPase molecules," Biochemistry 45:3117–3124 ("Biochemistry 2006"). (both articles attached).

The inventors' novel work was also recognized in an article reporting work lead by Prof. M. A. El-Sayed of the Georgeia Institute of Technology. Quoting Dr. El-Sayed: "Single molecular DNA detection was also reported using dark field microscopy of **gold nanorod sensors** linked to F1-ATPase motors.[290]" (Xiaohua Huang, Svetlana Neretina, and Mostafa A. El-Sayed, Gold Nanorods: From Synthesis and Properties to

Biological and Biomedical Applications Adv. Mater. 2009, 21, 4880–4910 (emphasis added)) Where the reference [290] is to J. York, D. Spetzler, F. Xiong, W. D. Frasch, Lab Chip 2008, 8, 415 (both articles attached for reference).

The Lab Chip 2008 article has been cited by at least 4 other papers. Similarly, many others have recognized the original work of the applicants in the area of using gold nanorods for rotation measurements in molecular motors. As evidenced by the Google Scholar® searches attached. For example the Biochemistry 2006 publication has been cited by at least 15 references according to Google Scholar (Search attached). The same search indicated that other articles co-authored by the inventors have been cited by at least 16 other scholarly references.

The long felt and unsolved need for the claimed invention is further evidenced by acceptance of an article authored by Sonnichsen, "Gold Nanorods as ***Novel*** Nonbleaching Plasmon-Based Orientation Sensors for Polarized Single-Particle Microscopy," *Nano Lett.*, **2005**, *5* (2), pp 301–304 (attached, emphasis added). According to the abstract:

> By monitoring the polarized light scattering from individual **gold nanorods** in a darkfield microscope, we are able to determine their orientation as a function of time. We demonstrate time resolution of milliseconds and observation times of hours by observing the two-dimensional rotational diffusion of **gold rods** attached to a glass surface. The observed orientational diffusion shows a fast component of about 60 ms and "sticky times" of seconds. The large signal-to-noise ratio, chemical and photochemical stability, fast time response, and small size of these gold nanorods make them an ideal probe for orientation sensing in material science and molecular biology. (emphasis added)

Note that Sonnichsen published this article in 2005 while the instant application has priority back to a provisional application filed in 2002, three years earlier. Sonnichsen does not recognize the added benefits of rotation of the gold rods yet he terms their use as a sensor as "novel." Sonnichsen's "novel" use of gold rods is accepted by the scientific community as evidenced by 87 citations according to Google

Scholar. The novel term is used despite the fact that the article itself cites Yasuda at page 304 ("(12) Yasuda, R.; Noji, H.; Yoshida, M.; Kinosita, K.; Itoh, H. *Nature* **2001**, *410*, 898."). It is clear from the acceptance of the publications of Sonnichsen and the instant invention that nanorods are recognized by the scientific community as a significant advance over gold discs.

Note that the instant inventors filed their first application about 3 years *before* Sonnichsen, which has been widely accepted. This is striking evidence of a long felt and unsolved need to find a method for single molecule detection in the form of a gold nanorod.

Therefore, when the Graham factors are taken into account, the instant invention must be found non-obvious and allowable over the references. There was a long-felt and unsolved need for the invention and the solution, gold nanorods attached to a molecular motor, have been widely accepted by those working in the field. The instant inventors were the first to teach the use of the nonanrods for rotation detection. The facts bear out that the amended Claims 40,42-47,49-54 and 56-60 are allowable over the references whether taken singly or in any combination.

Claims 40,42-47,49-54 and 56-59 are non-obvious and patentably distinct over U.S. Patent No. 6,989,235

Claims 40-59 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 6,989,235 in view of Sonnichsen (Physical Review Letter Pub 112002) (as evidenced by Mock (Nano Letters Pub 412002)) and Pettingell et al (US Patent 6449088 Filed 1993). Claims 41, 48 and 55 are canceled.

U.S. Patent No. 6,989,235 uses nanospheres or beads and not nanorods. As shown in the argument above the discovery of the rotational properties of nanorods supplies an answer to a long felt unsolved need in the art. Also as shown above neither Sonnichsen. Mock or Pettingell supply this essential element. Therefore, Claims 40-59 are patentable over U.S. Patent No. 6,989,235 in view of Sonnichsen (Physical Review

Letter Pub 112002) (as evidenced by Mock (Nano Letters Pub 412002)) and Pettingell et al (US Patent 6449088 Filed 1993) whether taken singly or in any combination.

Provisional double patenting rejection is moot

Claim 40-59 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 10582820 in view of Sonnichsen (Physical Review Letter Pub 112002) (as evidenced by Mock (Nano Letters Pub 412002)) and Pettingell et al (US Patent 6449088 Filed 1993). Claims 41, 48 and 55 are canceled.

A terminal disclaimer is filed herewith with the applicable fee to overcome the double patenting rejection relating to copending Application No. 10582820.

Claim 60 is allowable because the cited art does not teach every element

For a claim to be found obvious in view of the references, all of the claim elements must be found in a properly combined set of references. Here the references do not disclose all of the claimed elements of the invention as set out in amended claim 60. In particular, the references fail to disclose at least the element of disposing a detection DNA strand between the nanoparticle and the molecular structure, wherein the detection DNA strand hybridizes with a target DNA strand such that if the target DNA strand matches the detection DNA strand *they form a structural link between the molecular structure and the nanoparticle causing the nanoparticle to rotate.*

Yasuda is cited for disclosing attaching a nanobead to an F1 ATPase motor, rotation using a nanobead and imaging with laser. However, Yasuda shows bonding to a rotating arm with biotin and streptavidin and no target matching DNA linkage is shown.

Sonnichsen is cited for disclosing gold nanorods. As evidenced by Mock a property of a nanorod is to alternately produce red and green polarized light when illuminated with polarized white light along the axes. No target matching DNA linkage is shown in Sonnichsen or Mock.

As stated above, Felder is cited for disclosing oligonucleotide links as an anchor. No target matching DNA linkage between a rotating molecular motor and a nanoparticle suitable for causing the nanoparticle to rotate is discussed. However, Felder differs strikingly from the instant invention for many reasons. As one example, Felder requires "a surface comprising multiple spatially discrete regions, at least two of which are substantially identical..." (Claim 1). No such spatially discreet regions are required in the present invention. In fact Felder needs multiple copies of these spatially discreet regions as stated in his specification "The spatially discrete regions of the invention are present in multiple copies. That is, there are at least two, preferably at least twenty, or at least about 24, 50, 96, 256, 384, 864, 1536, 2025, or more, etc.," (See, for example, Fig. 1 and Fig. 2). Felder does not address molecular motors or gold nanorods. Given that only the present invention teaches linking in order to effect rotation of gold nanorods, the present invention including claims 40,42-47,49-54 and 56-60 are patentable over the references whether taken singly or in any combination.

Greenberg discloses a polarizing filter and does not otherwise supply claimed elements missing in the disclosures of the other references.

Claim 60 is allowable over the references because none of the references, whether taken singly or in any combination, teach the claimed feature that a structural link suitable for rotating a nanoparticle linked to a molecular motor is created by the hybridization of a detection strand and a DNA target strand.

For these reasons, and in view of the above amendments, this application is now considered to be in condition for allowance and such action is earnestly solicited.

Respectfully Submitted,

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